C-reactive protein and familial risk for dementia

A phenotype for successful cognitive aging

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ABSTRACT

Objectives: Identifying phenotypes for successful cognitive aging, intact cognition into late-old age (>age 75), can help identify genes and neurobiological systems that may lead to interventions against and prevention of late-life cognitive impairment. The association of C-reactive protein (CRP) with cognitive impairment and dementia, observed primarily in young-elderly samples, appears diminished or reversed in late-old age (75+ years). A family history study determined if high CRP levels in late-old aged cognitively intact probands are associated with a reduced risk of dementia in their first-degree family members, suggesting a familial successful cognitive aging phenotype.

Methods: The primary sample was 1,329 parents and siblings of 277 cognitively intact male veteran probands at least 75 years old. The replication sample was 202 relatives of 51 cognitively intact community-ascertained probands at least 85 years old. Relatives were assessed for dementia by proband informant interview. Their hazard ratio (HR) for dementia as a function of the proband's log-transformed CRP was calculated using the proportional hazards model.

Results: Covarying for key demographics, higher CRP in probands was strongly associated with lower risk of dementia in relatives (HR = 0.55 [95% confidence interval (CI) 0.41, 0.74], $p < 0.02$). The replication sample relationship was in the same direction, stronger in magnitude, and also significant (HR = 0.15 [95% CI 0.06, 0.37], $p < 0.0001$).

Conclusions: Relatives of successful cognitive aging individuals with high levels of CRP are relatively likely to remain free of dementia. High CRP in successful cognitive aging individuals may constitute a phenotype for familial—and thus possibly genetic—successful cognitive aging. *Neurology*® 2012;79:1116-1123

GLOSSARY

AD = Alzheimer disease; **CDR** = Clinical Dementia Rating; **CI** = confidence interval; **CPRS** = Computerized Patient Record System; **CRP** = C-reactive protein; **CVRF** = cardiovascular risk factor; **HR** = hazard ratio; **JJP-VAMC** = James J. Peters Veterans Affairs Medical Center; **MMSE** = Mini-Mental State Examination.

Most studies supporting associations of cardiovascular risk factors (CVRFs) with increased risk of subsequent cognitive decline, dementia, and Alzheimer disease (AD)¹ derive from young-elderly (<75 years) cohorts. Longitudinal studies at older ages are inconsistent, with some associations in the opposite direction.²⁻⁵ Focusing on successful cognitive aging, remaining cognitively intact into late-old age (>age 75), might help explain these discrepancies. A CVRF associated with subsequent poor cognitive outcome based on young-elderly samples may be called a “putative” risk factor for those in late-old age because generalization would be plausible. Conversely, prevalent successful cognitive aging in those with this putative risk factor may be attributable to countervailing factors—perhaps familial—promoting successful cognitive aging. The putative risk factor in individuals with successful cognitive aging would be testable

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Supplemental Data

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as a phenotype for successful cognitive aging by examining the extent of successful cognitive aging among their relatives.

C-reactive protein (CRP) is a biomarker for systemic inflammation and a CVRF.⁶ In longitudinal studies of cognitive healthy subjects at baseline, significant relationships with impaired cognitive function were observed for young cohorts (averaging ≤ 63 years),^{7–9} but not old cohorts (≥ 77),^{10–13} with mixed results for intermediate cohorts (71 and 74 years).^{11,14–18} Moreover, our group found higher levels of CRP associated with better memory function in cognitively intact individuals over age 75.¹⁹ The present study evaluated high CRP as a phenotype for successful cognitive aging by testing the hypothesis that a higher CRP in successful cognitive aging probands is associated with less dementia in parents and siblings.

METHODS **Probands.** The primary convenience sample consisted of cognitively intact, 75+ year old, male veteran outpatients at the JJP-VAMC in the Bronx, New York, enrolled from 2004 through 2010. The Computerized Patient Record System (CPRS) was used for an initial screen to exclude patients carrying a diagnosis of dementia, neurodegenerative disorder (e.g., Parkinson disease), or psychosis, or a history of cerebrovascular accident. Also excluded, regardless of diagnosis, were those prescribed dementia-related medications (e.g., donepezil). Letters were sent to potentially eligible subjects. Volunteers were then assessed both directly and through informants to ensure eligibility (see below). Many of these subjects were also participants in other studies.^{19,20}

Demographics, medical chart review, and health questionnaire. Collected demographic and health-related information on the probands included age, years of education, marital status, occupation (their own, their spouse's, their father's), and physical activity level across each decade of their adult life. The CPRS provided diagnoses of specific illnesses, particularly diabetes and hypertension. Probands reported on history of tobacco smoking, head injury, and major depression or other serious mental illnesses.

Verification of intact cognition in probands. The Clinical Dementia Rating scale (CDR)²¹ assessed 6 domains of cognitive function with probands and with their informants to rate global dementia status. Probands were required to have CDR = 0, indicating absence of even questionable dementia, and also a Mini-Mental State Examination (MMSE)²² score better than the 10th percentile of age- and education-adjusted norms.²³ The intact cognitive status of each potential proband was then determined by a clinical consensus conference led by M.S. or H.T.G., both blind to CRP level and family dementia history.

Blood assays. Probands provided a fasting blood sample for assessment of high sensitivity CRP, in serum using the ADVIA 1650 Chemistry System with a CRP latex reagent, and other CVRFs (e.g., cholesterol, hemoglobin A1c). DNA was extracted

and *APOE* was genotyped to identify those with an $\epsilon 4$ allele. CRP was not normally distributed (skewness = 2.60, kurtosis = 7.40), so the usual logarithmic transformation was employed (skewness = -0.36 , kurtosis = -0.49). For descriptive purposes, CRP was categorized into tertiles.

Demographic and cognitive information collection on relatives. Only parents and siblings of the probands were included in the analyses, since they—but not offspring—were typically elderly. The AD Risk Questionnaire²⁴ was administered to probands to collect information on each relative's birth year, sex, and age (at time of interview or death), and to screen for memory loss or other cognitive. Diagnosis of dementia and age at onset were established by the Dementia Questionnaire administered to the proband.

Statistical methods. We used the proportional hazards model in the *R* survival analysis package,²⁵ to evaluate the risk for incident dementia in relatives as a function of their age at onset of dementia. It takes into account the diminishing number of relatives at risk due to censorship by prior death or dementia morbidity, or age at assessment of no dementia status. The package provides robust correction for lack of independence within clusters, so family membership was always included as a random factor in the model. The primary model assessed the association of risk with log-transformed proband CRP—the HR, proband's age, proband's years of education, and relative's sex were additional covariates. We verified the proportional hazards assumption that risk functions for different values of a covariate (including log-transformed CRP) are proportional.²⁵ Additional analyses considered a quadratic CRP model; other covariates, including proband's *APOE* $\epsilon 4$ status; interactions of CRP with covariates; and subgroups of relatives.

Since there was a single primary hypothesis of association of proband CRP with risk of dementia in relatives, there was no adjustment of its level of significance for multiple comparisons. The Holm procedure for multiple comparisons,²⁶ an enhancement of the Bonferroni procedure, was employed to evaluate the results of additional analyses involving covariates, interactions, and subgroups.

Replication sample. An independent convenience sample of 85+ year old cognitively intact, community-dwelling probands was ascertained between 2004 and 2010 in the New York area. The same primary and additional analyses as the primary sample were performed, except analyses of relatives of probands with *APOE* $\epsilon 4$, since there were too few. The sex of the proband was an additional covariate. These subjects, described in detail elsewhere,²⁷ were recruited after talks on memory at senior centers, through newspaper advertisements, and word of mouth. Those without memory concerns were encouraged to volunteer, and were assessed using the same cognitive, family, and blood assessments as the veteran sample. Cognitive status was confirmed in the same consensus conferences as the veterans, but without routine access to medical records.

Standard protocol approvals, registrations, and patient consents. The study was approved by institutional review boards of the Mount Sinai School of Medicine and the James J. Peters Veterans Affairs Medical Center (JJP-VAMC), with probands providing written informed consent.

RESULTS Information on relatives and CRP levels were collected on 277 probands from the JJP-VAMC. Table 1 shows characteristics of all probands

Table 1 Characteristics of late-old aged cognitively intact male veterans and their relatives

		CRP tertiles			
Characteristic	Total sample	Low (0.00–0.33)	Middle (0.34–1.58)	High (1.61–16.70)	Statistical test, <i>p</i> value
Probands without dementia					
No.	277	93	92	92	
Age, <i>y</i> (SD)	81.3 (4.2)	80.8 (4.4)	81.8 (4.0)	81.4 (4.3)	$F_{2,274} = 1.37, p = 0.26$
Education, <i>y</i> (SD)	14 (3)	14 (4)	14 (3)	14 (3)	$F_{2,274} = 0.28, p = 0.76$
CRP, mg/L (SD)	1.89 (2.85)	0.14 (0.10)	0.81 (0.37)	4.73 (3.46)	
Log _e CRP (SD)	−0.149 (0.765)	−1.028 (0.431)	−0.149 (0.201)	0.636 (0.372)	
APOE genotype, <i>n</i> (%)	252 (91.0)	86 (92.5)	85 (92.4)	81 (88.0)	
ε2/ε2	3 (1.2)	0 (0)	0 (0)	3 (3.7)	$\chi^2 = 16.84, df = 10, p = 0.078$
ε2/ε3	31 (12.3)	11 (12.8)	12 (14.1)	8 (9.9)	
ε2/ε4	7 (2.8)	3 (3.5)	3 (3.5)	1 (1.2)	
ε3/ε3	171 (67.9)	55 (64.0)	54 (63.5)	62 (76.5)	
ε3/ε4	38 (15.1)	17 (19.8)	14 (16.5)	7 (8.6)	
ε4/ε4	2 (0.8)	0 (0)	2 (2.4)	0 (0)	
1 + ε4 allele	47 (18.7)	20 (23.3)	19 (22.4)	8 (9.9)	$\chi^2 = 6.08, df = 2, p < 0.05$
Relatives (parents and siblings)					
No.	1,329	456	448	425	
Average family size (SD)	4.8 (2.5)	4.9 (2.5)	4.9 (2.7)	4.6 (2.2)	$F_{2,276} = 0.36, p = 0.70$
Age, <i>y</i> (SD)	71.9 (18.8)	71.1 (20.2)	72.5 (17.2)	72.2 (18.9)	$F_{2,1326} = 0.69, p = 0.50$
Female, <i>n</i> (%)	643 (48.4)	199 (43.7)	235 (52.5)	209 (49.2)	$\chi^2 = 7.01, df = 2, p = 0.03$
Cases of dementia	40	18	14	8	
Onset of dementia	79.7 (8.2)	78.8 (9.1)	81.2 (6.9)	79.6 (9.0)	

Abbreviation: CRP = C-reactive protein.

and relatives, and for each CRP tertile. Sixty percent of probands in the high tertile had values above the normal limit, 3.0 mg/L. There were no significant tertile differences in proband age or proband years of education. *APOE* genotyping was performed for 259 of the 277 probands, with fewer *APOE* ε4 carriers found in the highest tertile. We found no differences among proband tertiles in marital status, physical activity level, tobacco use, total cholesterol, triglycerides, hemoglobin A1c, diastolic or systolic blood pressure, the proband's occupation, the spouse's occupation, the father's occupation, the presence of diabetes, hypertension, head injury, or major depression. The relatives of probands in each tertile had similar ages, but there were more males in the lowest tertile.

Dementia was identified in 40 relatives from 37 families (3 with 2 cases each). Results from proportional hazards models are presented in table 2. In the primary model, there was significantly decreasing risk of dementia in relatives as proband CRP increased, but no significance of the other primary model covariates. The result excluding the 3 other covariates was similar. Addition of quadratic CRP to the model was not significant. Proband *APOE* ε4 status was not a significant covariate, and adding it

did not change the association with CRP. No interactions of proband CRP with any of these covariates were significant.

Subsidiary analyses examined the HR for CRP in subgroups of relatives. HRs were similar to the overall result for parents, siblings, and relatives of probands with and without *APOE* ε4; their lack of significance was attributable to the smaller samples and the more stringent Holm significance criterion. CRP spikes in the presence of some acute and chronic inflammatory conditions excluding the 9 families of probands with CRP >10.0 mg/L did not essentially change the HR for CRP.

We tested whether a higher proband CRP level was associated with greater mortality in relatives, because a reduced rate of dementia might be explained by differentially greater censorship due to mortality among those relatives putatively most vulnerable to dementia. However, replacing dementia by mortality in the primary model, the association of CRP with mortality risk in relatives was not significant, and nominally protective (HR = 0.94 [95% CI 0.084, 1.04], $z = -1.11, p = 0.24$).

For descriptive purposes, we constructed dementia cumulative risk curves for each tertile using the

Table 2 Proportional hazard model results for primary and additional models in the primary and replication samples

Factor ^{a-c}	No.	Cases	Hazard rate	95% CI	Z	p
Primary sample						
Primary model						
CRP	1,329	40	0.55	0.34, 0.89	-2.41	0.02 ^d
Relative's sex	1,329	40	1.29	0.68, 2.42	0.78	0.39
Proband's years of education	1,329	40	1.04	0.96, 1.13	1.14	0.25
Proband's age	1,329	40	1.05	0.98, 1.12	1.32	0.19
Additional analyses						
CRP (no other covariates)	1,329	40	0.56	0.36, 0.89	-2.48	0.01
CRP quadratic term	1,329	40	1.15	0.76, 1.74	0.66	0.51
CRP (with proband APOE ε4 status covariate)	1,215	39	0.58	0.35, 0.96	-2.12	0.03
CRP × relative's sex	1,329	40	0.77	0.31, 1.93	-0.56	0.58
CRP × proband's years of education	1,329	40	0.93	0.80, 1.06	-1.04	0.30
CRP × proband's age	1,329	40	1.08	0.99, 1.17	1.84	0.07
CRP × APOE ε4 status	1,215	39	0.96	0.31, 2.94	-0.07	0.94
CRP (parents only)	527	14	0.56	0.28, 1.10	-1.68	0.09
CRP (siblings only)	802	26	0.53	0.27, 1.03	-1.87	0.06
CRP (only APOE ε4-)	972	31	0.58	0.33, 1.03	-1.86	0.06
CRP (only APOE ε4+)	243	8	0.53	0.17, 1.69	-1.07	0.28
CRP (excluding CRP >10.0 mg/L)	1,286	40	0.58	0.35, 0.97	-2.10	0.04
Replication sample						
Primary model						
CRP	202	9	0.15	0.06, 0.37	-4.05	<0.0001 ^d
Relative's sex	202	9	7.56	0.85, 67.1	1.82	0.07
Proband's years of education	202	9	1.07	0.84, 1.36	0.55	0.58
Proband's age	202	9	0.91	0.84, 0.99	-2.18	0.03
Additional analyses						
CRP (no other covariates)	202	9	0.18	0.09, 0.38	-4.55	<0.0001 ^e
CRP quadratic term	202	9	0.006	0.00, 1.40	-1.86	0.07
CRP (with proband APOE ε4 status covariate)	190	9	0.16	0.06, 0.41	-3.80	<0.0001 ^e
CRP × relative's sex	202	9	0.66	0.26, 1.67	-0.87	0.38
CRP × proband's years of education	202	9	0.92	0.74, 1.14	-0.78	0.43
CRP × proband's age	202	9	0.84	0.74, 0.94	-2.91	0.004 ^e
CRP (parents only)	100	5	0.24	0.10, 0.53	-3.47	0.0005 ^e
CRP (siblings only)	102	4	0.11	0.04, 0.37	-3.65	0.0003 ^e
CRP (only APOE ε4-)	140	8	0.15	0.06, 0.38	-4.01	<0.0001 ^e
CRP (proband's sex covariate)	202	9	0.14	0.05, 0.37	-4.00	<0.0001 ^e
CRP × proband's sex	202	9	0.19	0.03, 1.23	-1.74	0.08
CRP (proband males only)	69	2	0.68	0.18, 2.49	-0.60	0.56
CRP (proband females only)	133	7	0.06	0.01, 0.56	-2.46	0.014

Abbreviations: CI = confidence interval; CRP = C-reactive protein.

^a All models include family as a cluster variable and, except for the "no other covariates" model, all the primary model variables.

^b CRP is always log-transformed proband CRP.

^c A model testing an interaction with CRP also includes the other variable of the interaction.

^d Significant ($p < 0.05$) without Holm adjustment for multiple comparisons.

^e Significant ($p < 0.05$) by the Holm procedure, separately for the 2 samples.

Figure 1 Cumulative risk of dementia in relatives of cognitively intact male veteran probands aged 75+ by proband C-reactive protein (CRP) tertile

Risk curve for relatives of the low CRP tertile group is the solid brown line with red squares. Risk curve for relatives of the middle CRP tertile group is the solid yellow line with green triangles. Risk curve for relatives of the high CRP tertile group is the blue dotted line with open circles.

actuarial life table method. By age 90, the cumulative risks were 0.13, 0.12, and 0.05 for relatives of probands in the low, middle, and high tertiles (figure 1). Discrepancies are small below age 80, but the proportional hazards assumption is not substantively violated because all rates are very low.

In the replication sample, the 51 probands had 202 parents and siblings (table e-1 on the *Neurology*® Web site at www.neurology.org provides descriptive statistics). As in the primary sample, higher CRP was associated with lower risk of dementia in relatives, but this result was more strongly significant ($p < 0.0001$; table 2). None of the other covariates in the primary model achieved significance by the Holm criterion, and the risk for CRP was not substantially affected by excluding the 3 other covariates. Addition of quadratic CRP to the model was not significant; proband *APOE* $\epsilon 4$ status was not a significant covariate and it did not affect the CRP association.

For all the subgroups considered for the primary sample, the replication sample hazard rates were not substantially different from the overall hazard rate in the replication sample, and were also statistically significant. There was a significant interaction between CRP and proband's age, but—as for the primary sample—interactions of CRP with relative's sex and proband's years of education were not significant. In the primary sample, all probands were male; the hazard rate for relatives of male probands in the replica-

tion sample was similar to the hazard rate in the primary sample. Although the hazard rate for relatives of female probands in the replication sample was nominally smaller, the interaction of proband sex with CRP was not significant. Inclusion of proband sex as a covariate did not change the association with CRP.

DISCUSSION For the primary sample of cognitively intact, late-old aged (75+ year old) male veterans, high proband CRP level was significantly associated with low dementia risk in their relatives. The relationship was stronger in a smaller, independent, community-ascertained sample of cognitively intact, even older (85+ year old) probands. The similar direction of these results—despite several differences between the samples—nominates high CRP in individuals with successful cognitive aging as a phenotype for familial successful cognitive aging.

For some other CVRFs, putative risk factors in late-old age subjects are associated with their own lower risk of subsequent decline; both samples in this study showed this for risk in relatives. By what mechanism might a risk factor associated with a deleterious effect in young-elderly be associated with a reduced or protective effect in late-old age? Several investigators have proposed that protective genotypes or other protective factors may “buffer” the effects of risk factors, and aging per se, on dementia and death.^{28,29} A person with such protection may better tolerate the destructive associations of a specific risk factor with both longevity and cognition. The effect on longevity may influence the apparent effect on cognition.

Figure 2 shows a survivor effect model with disparate distributions at different ages of a putative risk factor for protected and nonprotected subjects with intact cognition. By early old age (left side), the risk factor has not yet reached the critical period for the bad outcomes of cognitive decline and death. Thus, those with intact cognition consist of an unprotected majority (red) and a protected minority (blue), with a wide range of risk factor levels in both groups. Over time, CVRF associations with death and cognitive impairment will be readily observed because there are many more unprotected than protected subjects. By late-old age (right side), the protected and unprotected groups have different distributions of the risk factor, due to differential censorship effects of mortality and cognitive impairment. The reduced number of unprotected individuals surviving with intact cognition will tend to have low risk factor levels, which contributed to their survival and intact cognition. In contrast, protected subjects are more likely to survive, and to have intact cognition, even at high

Figure 2 The survivor effect model

The left side represents unprotected (red) and protected (blue) cognitively intact individuals in midlife and early old age and shows both groups with a wide range of risk factor levels. The right side represents unprotected (red) and protected (blue) individuals in late-old age where the unprotected group (red) has disproportionately fewer survivors and those who do survive tend to have lower levels of risk factors. The protected group (blue) has minimal attrition due to mortality and dementia regardless of the risk factor level.

risk factor levels. Thus, survivors with intact cognition include relatively more protected individuals than at younger ages. Moreover, proportionately more protected than unprotected survivors have high risk factor levels, unlike at younger ages.

In this survival model, at midlife, most subjects will be the more common, unprotected individuals, for whom the risk factor will predict poor subsequent cognition. By late life, unprotected survivors will have risk factor levels that are lower than the midlife population, but those with highest risk factor levels will have highest dementia risk. In contrast, the protected survivors will have low risk of dementia despite a full range of risk factor levels. The increasingly larger proportion of protected individuals, and the lower risk factor levels in unprotected individuals, will reduce the predictive impact of the risk factor.^{2–5,30} When the unprotected survivors have higher dementia risk and lower risk factor levels than the protected survivors, the association of the high risk for dementia with lower risk factor levels will reverse the association observed in midlife. Such a reversal of association has been reported for some CVRFs.^{2–5,30}

As noted above, longitudinal studies of late-old age subjects with no cognitive impairment have not found associations of high CRP with increased or decreased risk for subsequent decline. In apparent contrast, a cross-sectional analysis of dementia in nonagenarians showed higher CRP levels in those with dementia.³¹ According to the survivor effect model, survivors with dementia would be relatively likely to be unprotected individuals with high risk factors. Moreover, a parallel analysis of incident dementia

from the same project showed no association with CRP level.³² Although the model in figure 2 might predict a negative association of CRP with dementia risk at age 90, this refers to cognitively intact survivors. Almost half of the nonagenarian sample without dementia (44%) were cognitively impaired, and thus more likely to be unprotected than cognitively intact survivors. This might increase their association of CRP with dementia risk, counteracting the association in the cognitively intact subjects.

CRP is a biomarker for inflammation, which is generally associated with increased risk of poor cognitive outcomes,³³ so the association of CRP with risk of dementia in relatives may not reflect a mechanism involving CRP per se. In contrast to young elderly subjects, in 86+-year-old subjects, genes associated with dementia regulated inflammatory and immune function; in cognitively intact subjects' brains, immune response genes were upregulated, and downregulated in subjects with dementia.³⁴ That study raises the possibility that a more active immune system may have a protective role against dementia specifically in the very old. The CRP findings of the present study are consistent with the relevance of a robust immune function in the very old without dementia, and a familial—and thus possibly genetic—effect.

As seen elsewhere,³⁵ the *APOE* $\epsilon 4$ allele was less common among the probands in the highest tertile, suggesting a possible association of dementia risk with relatives' *APOE* $\epsilon 4$ status. The relationship of high proband CRP with low dementia risk in relatives was similar after adding proband *APOE* $\epsilon 4$ status as a covariate, and in the 2 subgroups of relatives by proband *APOE* $\epsilon 4$ status. Thus, we found no indication that the CRP/familial risk association is attributable to a possible discrepancy of relatives' *APOE* $\epsilon 4$ status.

Our study raises methodologic issues requiring consideration. The primary proband sample was comprised only of men, but the older replication sample included both sexes. In the smaller replication sample, the HR for males was similar to the primary sample, and for females it was nominally lower. This suggests that the CRP association observed in the primary sample is not limited to males.

The number of cases is small because the rate of dementia in relatives of late-old aged cognitively intact probands is lower than in the general population.²⁰ Direct assessment of relatives would have enhanced the study, but our method has demonstrated very good reliability^{36,37} and validity.^{38,39} Improving on the reliability studies, the proband informant was always a contemporary of the rela-

tives. Direct assessment of all living relatives would be logistically challenging and expensive.

Direct examination of the living relatives would also have permitted measuring their CRP level, but this intervening variable was not critical for the model of association of proband CRP with dementia risk in relatives. The relative's own years of education was not consistently available, so this was not included as a control variable. Among the probands, the partial correlation of years of education and CRP, controlling for age, was small (partial $r = 0.07$, $p = 0.24$), suggesting that an association of relatives' CRP with their education is unlikely to be strong enough to account for the association between high proband CRP and low risk for dementia in relatives.

The association between relatively high CRP levels in cognitively intact late-old aged probands and low risk of dementia in relatives links the familiarity of successful cognitive aging with discrepant impact of CRP on risk of cognitive decline at different ages. Indeed, other than age itself,^{20,40} characteristics distinguishing among late-old aged probands without dementia—who therefore demonstrate successful cognitive aging—have not to our knowledge previously distinguished extent of risk for dementia among their relatives. Similar examination of relatives using other CVRFs in the primary proband group will be conducted. This study suggests that, among such probands, relatively high levels of CRP may be a useful biological phenotype for familial successful cognitive aging. This phenotype may help identify relevant genes, leading to development of interventions for maintaining cognitive function.

AUTHOR CONTRIBUTIONS

Study concept and design: Dr. Silverman. Analysis or interpretation of data: Drs. Silverman, Schmeidler, Beeri, Rosendorff, Sano, and Haroutunian. Drafting/revising the manuscript for content: Drs. Silverman, Schmeidler, Beeri, Grossman, Carrión-Baralt, Bernalova, and Bernalova, R. West, and Dr. Haroutunian. Statistical analysis: Drs. Silverman and Schmeidler. Obtaining funding: Drs. Silverman and Haroutunian.

DISCLOSURE

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